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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/078,531	02/21/2002	Denis Martin	PHARMA-18	3055

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EXAMINER	
SHAHNAN SHAH, KHATOL S	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/078,531	MARTIN ET AL.	
	Examiner	Art Unit	
	Khatol S Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-16,22-29 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-21 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-34* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 February 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8,9 and 2/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment received 06/11/2002 is acknowledged. Specification pages 3 and 27 have been amended.

2. Applicant's amendment received 10/30/2002 is acknowledged. Specification page 1 has been amended. Claims 21 and 26-29 have been amended. New claims 30-34 have been added.

Election/Restrictions

3. Applicants' election with traverse of February 27, 2004, is acknowledged. Applicants elected Group III claims 17-21 and 30 which are drawn to a polypeptide. Applicants further elected polypeptide species of claim 17 (a).

The traversal is on the ground that it would not be a serious burden on the examiner to examine multiple groups because all claims of this application involve related subject matter, has been noted. This is not found persuasive because while the searches may overlap, they are not coextensive. As stated in the restriction requirement, groups II, IV, V, VI and VII are drawn to different methods which differ in method objectives, steps, reagent and material used. Groups I, III and VIII are drawn to structurally and functionally distinct compositions.

The requirement is still deemed proper and is therefore made **FINAL.**

4. Currently claims 1-34 are pending.

5. Claims 1-16, 22-29 and 31-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions.

6. Claims 17-21 and 30 are under consideration.

Information Disclosure Statement

7. Applicants' information disclosure statements of 6/21/02, 3/4/03 and 2/27/04 are acknowledged. The examiner has considered the references. See attached form 1449s.

Drawings

8. This application, lacks formal drawings. The informal drawings filed in this application are acceptable for examination purposes. When the application is allowed, applicant will be required to submit new formal drawings. It has been noted that Figure 3 labeling is incorrect. Figure 3 flows into several pages and should be labeled as Fig 3A, 3B, 3C and 3D etc. Appropriate corrections are required.

Specification

9. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. (see page 2 and amended page 27). Applicants are required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Appropriate correction is required.

10. The use of the trademarks (i.e. QuilA, QS21, Alhydrogel etc) have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

11. ATCC address on pages 26 and 32 of the specification is incorrect or not current. Appropriate correction is required.

Claim Objections

12. Claims 19 and 20 are objected to because of the following informalities:

The claims recite, "polypeptides are linked to formed a chimeric polypeptides". Appropriate corrections are required.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 17-21 and 30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-22 of copending Application No. 10/476,614. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims of both applications are drawn to a polypeptide chosen from SEQ ID NO: 2 or fragments and analogs thereof. No restriction to the size of these fragments has been made in the claims. One of the embodiments of claims 17 and 18 of the instant application is " a polypeptide chosen from SEQ ID NO: 2 or fragments and analogs thereof". Claims 18 and 19 of Application No. 10/476,614 recite the same embodiment and SEQID NO: 2 of Application No. 10/476,614 has 74.4% sequence identity to SEQID NO: 2 of the instant application (see sequence alignment). Claims 19 and 20 of the instant application

recite a chimeric polypeptide of SEQ ID NO: 2 or fragments and analogs thereof". Claims 20 and 21of Application No. 10/476,614 recite the same embodiments. Finally claims 21 and 30 of instant application recite a pharmaceutical composition. Claim 21 of Application No. 10/476,614 also recites a pharmaceutical composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 17-21 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising SEQ ID NO: 2, does not reasonably provide enablement for analogs and fragments of a sequence at least 70% identical to SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP) 2164.01(a). Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples (6) the quantity of experimentation, (7)

the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are drawn to isolated polypeptides comprising amino acid sequences which are at least 70% identical to SEQ ID NO: 2. Fragments and analogs from these variant sequences are also claimed. These terms can encompass as few as one or more amino acids. Additionally, a fragment or an analog derived from an amino acid sequence which varies by as much as 30% identity from SEQ ID NO: 2 can encompass fragments with nothing in common with SEQ ID NO: 2 i.e., the fragment or analog could be taken from the 30% of the sequence which is different from SEQ ID NO: 2.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species.

The breadth of the instant claims is drawn to polypeptides, which are not specified in the sequence disclosure. The specification states that substitutions, additions or deletions may be to the defined sequences (see page 9, lines 6-10); however the specification provided no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g. such as various positions or regions directly involved in

binding, catalysis in providing the correct three- dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions.

The specification (page 1) recites that these polypeptides may be used to prevent, diagnose and /or treat streptococcal infection. It is unclear how the amino acid sequences are selected or how the skilled artisan would predict the sequences required to accomplish these required functions. The specification does not teach how one would make this selection or teach a method to predetermine the sequence structure for appropriate selection to result in the required affinity constant and antigenic specificity. The art teaches that even minor changes in the amino acid sequences may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function (see abstract and title). Substitution of amino acids into a known sequence as well as identifying and using fragments of proteins containing an isolated functional domain of a protein is within the realm of protein chemistry and is one of the most unpredictable areas of protein chemistry. For example Burgess et al. (J of Cell Biology, 1990 Vol. 111, pp. 2129-2138) teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Furthermore, Lazar et al (Molecular and Cellular Biology, 1988, Vol. 8, pp. 1247-1252) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid

substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

The instant claims are drawn to proteins comprising a sequence with a given percent similarity to a protein. Selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody, which is recognized by the native BVH-P7 protein on the *Streptococcus pyogenes* bacteria, and be ineffective in treating or preventing diseases or conditions caused by infection with *Streptococcus pyogenes*. Applicants have provided no guidance to enable one skilled in the art how to determine, without undue experimentation, the effect of different substitutions and the nature and the extent of the changes that can be made. In view of all of the above, in view of the lack of predictability in the art, and lack of guidance on how to obtain the desired fragments and analogs it is determined that it would require undue experimentation to make and/or use the claimed invention. In summary, the actual invention is not described in such a way that one skilled in the art could grasp the invention and make and/or use the invention and/or reproducibly practice the invention with a reasonable expectation of success, without undue experimentation. In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation

to make and use the invention commensurate in scope with the claims.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

18. Claims 17-21 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17-19 are vague and indefinite due to the phrase " or fragments or analogs thereof". A fragment can encompass as few as one amino acid. Additionally, the "fragment or analogs thereof" are derived from polypeptide sequences that vary by as much as 30% from the known sequences. The current claim language allows these sequences to be drawn from the portion of the sequences that is unknown because the claimed polypeptides are drawn to a percent identity of an amino acid, but do not require these variable sequences to have a function. The metes and bounds of the claimed molecule cannot be understood. It is not clear what is encompassed by " fragments or analogs thereof".

Claims 17-20 recite " an isolated polypeptide comprising a polypeptide chosen from" which renders the claim indefinite by reciting improper Markush language. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as Markush group, recites members as being " selected from group consisting of A, B and C". See Ex parte Markush, 1925 C.d. 126 (Comm'r Pat 1925). The claims lack either "and" or "or" between parts (f) and (g).

Claims 21 and 30 are indefinite as being dependent from indefinite claims 17 and 18.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 17-19, 21 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Bjorck et al. (WO 99/52939).

The claims are drawn to an isolated polypeptide chosen from a polypeptide comprising SEQ ID NO: 2 or fragments or analogs thereof.

Bjorck et al. teach an isolated polypeptide comprising a protein of *Streptococcus pyogenes* and its fragments or analogs thereof (see abstract and claims). Fragment containing residues 151-152 of protein H of *S. pyogenes* of the prior art matches a fragment containing residues 34-35 of SEQ ID NO: 2 of the instant application, residues 154-157 of protein H of *S. pyogenes* matches residues 627-630 of SEQ ID NO: 2 of the instant application and residues 159-162 of protein H of S. *pyogenes* matches residues 104-108 of SEQ ID NO: 2 of the instant application (see claim 1). The protein taught by Bjorck et al. is from *Streptococcus pyogenes* and it meets the limitation of "a fragment or analog" which are derived from the same organism. Bjorck et al. teach a chimeric polypeptide (see claim 8). With respect to the pharmaceutical composition, Bjorck et al. teach a pharmaceutical composition with an adjuvant and carrier (see claims 12-14). The prior art teaches the claimed invention.

Since the Office does not have the facilities for examining and comparing applicants'

composition with the composition of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed composition and the composition of the prior art (i. e., that the composition of prior art does not possess the same material structure and functional characteristics of the claimed composition). See In re Best, 562 F.2 d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol S Shahnan-Shah whose telephone number is (571)-272-0863. The examiner can normally be reached on 7:30am-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith can be reached on (571)-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Khatol Shahnan-Shah, BS, Pharm, MS

Art Unit 1645, May 12, 2004

RODNEY P SWARTZ, PH.D
PRIMARY EXAMINER